REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Claims 1-71 and 98-104 are presently pending. By this amendment, claims 3-15, 26, 39-43, 49-55, 57-67, 69-70, and 98-102 are canceled, and claims 1, 2, 23, 24, 27, 29, 30, 32, 34, 38, 44, 46, 48, 56, 68, 71, and 103 are amended to more clearly recite specific aspects of the invention. In addition, claim 105 has been added. Support for the amendments may be found throughout the claims and specification as originally filed, and the amendments do not constitute new matter. The amendments are not to be construed as acquiescence to any rejection and are made without prejudice to prosecution of any subject matter modified by amendment in a related divisional, continuation, or continuation-in-part application.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-71 and 98-104 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way a to enable one skilled in the art to make and/or use the invention. More specifically, the Action alleges that the claims are directed to a device for use in gene therapy, but the skilled artisan would not be able to use the claimed device without engaging in undue experimentation to devise a method of treatment. More specifically, the Action generally alleges that the invention is drawn to gene therapy for systemic delivery of a bioactive agent at therapeutic levels, but that given the highly unpredictable nature of gene therapy, the expectation of achieving a desired therapeutic effect using a claimed device is extremely low and would require undue experimentation.

Applicants respectfully traverse this basis of rejection and submit that the instant claims are fully enabled by the specification.

As a first matter, Applicants disagree with the Action's position regarding the nature of gene therapy methods involving transgene expression (as opposed to gene replacement) and submit that the skilled artisan could make and use the claimed invention without undue

experimentation. As repeatedly stated by the Federal Circuit, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), *citing Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), and *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). Indeed, the Court recognized that a considerable amount of experimentation may be required, so long as it does not amount to undue experimentation. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id., citing In re Jackson*, 217 USPQ 804 (Bd. App. 1982).

Applicants submit that the production of the claimed device and methods of using the same for systemic delivery of a bioactive agent would require only routine screening and experimentation and would not require undue experimentation on the part of the skilled artisan. Applicants submit that the specification provides adequate details and guidance regarding how to construct and combine each element of the claimed devices, including the biocompatible substance and the nucleic acid molecules. Furthermore, the specification clearly demonstrates effective cellular infiltration and gene expression using the claimed device (*see* Examples 1 and 2). Applicants submit that the production and optimization of the claimed devices would, therefore, only require merely routine optimization and testing, such as could be determined and performed by the skilled artisan using a variety of known methods. For example, the skilled artisan could readily prepare devices comprising nucleic acid constructs expressing a bioactive agent, implant these into a subject, and establish that the bioactive agent was expressed and systemically available at sufficient levels using routine antibody-based detection methods, such as, *e.g.*, ELISA.

Furthermore, regarding the Action's allegation that the instant specification does not demonstrate that therapeutic levels of the bioactive agent would be produced or systemically available, Applicants respectfully submit that there is no requirement that every embodiment be shown to be fully operative. Rather, Applicants submit that the existence of one or more inoperative species encompassed within the genus does not render claims to the genus non-enabled. *See, e.g., Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 224 U.S.P.Q. 409, 414

(Fed. Cir. 1984) stating that "[it is] not a function of the claims to specifically exclude possible inoperative substances." Furthermore, Applicants strongly disagree with the Action's contention that expression levels sufficient for systemic deliver of a bioactive agent would necessarily be of much greater magnitude and duration than those required for localized expression, as described in Roth *et al.* Applicants submit that the skilled artisan would appreciate that the desired amount of systemically available bioactive agent will vary depending upon the agent itself, as well as any modifications that have been introduced. For example, where an agent has been modified to target a specific cell, less systemic agent is required in order to introduce sufficient amounts of the agent to the cell. Also, the skilled artisan would appreciate that expression levels may be modulated though the use of different promoters, which drive expression at different levels. In addition, Applicants submit that the ability to express a transgene and regulate its levels of expression is clearly established in the art and is not unpredictable, as alleged by the Action.

Furthermore, Applicants submit that enablement of the claimed invention does not require a demonstration that the invention may be used therapeutically. Applicants submit that the Federal Circuit has clearly established that human clinical data sufficient to gain FDA approval is not required to establish patentability. In the landmark case of *In re Brana*, the Federal Circuit held that the FDA's requirements of testing for safety and effectiveness are not required by the patent laws. The Court stated, "[t]he Commissioner, as did the Board, confuses the requirement under the law for obtaining a patent with the requirements of obtaining government approval to market a particular drug for human consumption." 51 F.3d 1560, 1567 (Fed. Cir. 1995). The Court continued by stating that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. Applicants also note that the rejection described in *In re Brana* was made under Section 112 and not under Section 101.

In summary, Applicants submit that the presently claimed invention is fully enabled by the instant specification and that it would not require undue experimentation to use the invention as described in the specification for the systemic delivery of a bioactive agent. In addition, Applicants reiterate their position that there is no requirement to demonstrate

therapeutic efficacy of the claimed device. Accordingly, Applicants respectfully request that this basis of rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-6, 8, 9, 11-13, 23-26, 39-43, 49-55, 57-67, 69 and 98-104 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 95/22611 (the '611 application). More specifically, the Action alleges that the claims are directed to an *in situ* bioreactor adapted for systemic delivery of a bioactive agent, comprising (1) a first nucleic acid molecule encoding a cell growth stimulating agent, (2) a second nucleic acid molecule encoding a bioactive agent, and (3) a biocompatible substance capable of cellular infiltration. The Action further alleges that the '611 application discloses each of these elements and teaches that they can be combined and concludes that the '611 application, thus, teaches the *in situ* bioreactor of the instant application.

Similarly, claims 1-9, 11-15, 23-26, 39-43, 49-55, 57-67, 69, 70 and 98-104 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,962,427 (the '427 patent). The Action alleges that the '427 patent teaches each of the elements of the claimed *in situ* bioreactor and the combination of these elements, thereby teaching the *in situ* bioreactor of the instant application. In addition, the Action alleges that, absent evidence to the contrary, the devices described in both references are adapted for systemic delivery, since although the references do not recite any specific adaptions for such purpose, it appears the devices are capable of systemic delivery.

Applicants respectfully traverse these bases of rejection and submit that neither of the cited references teaches the claimed invention. Contrary to the Examiner's view, Applicants maintain their position that these references fail to disclose or describe an *in situ* bioreactor adapted for the **systemic** delivery of bioactive agents. Indeed, Applicants submit that the cited references provide absolutely no description or recognition that devices for the introduction of DNA into mammalian cells can be adapted or used for the systemic delivery of a bioactive agent.

Applicants submit that the '611 application merely describes a device for the localized delivery of an agent. More specifically, the '611 application is directed to devices for the localized introduction of nucleic acids into cells for the purpose of promoting bone growth,

or tissue repair and regeneration. The '611 application further teaches that the device is used to introduce nucleic acids into bone cells and tissues "at the area of bone fracture or damage that one desires to treat" (page 10, lines 27-30). Furthermore, in describing how to use the device, the '611 application states that it must be placed in contact with the site in the body in which one wishes to promote repair.

Regarding the '427 patent, Applicants submit that it is directed to a device implanted into a wound site that facilitates the transfer of DNA into mammalian repair cells localized at the wound site for the purpose of expressing a therapeutic protein that promotes healing of the wound (column 2, lines 21-32). Thus, the '427 patent is also clearly directed to a device for the localized delivery of a therapeutic agent. In fact, the '427 patent actually teaches away from the presently claimed invention, since it describes numerous disadvantages associated with the systemic delivery of therapeutic proteins (column 2, line 65 - column 3, line 10).

Nonetheless, without acquiescence to these bases of rejection and solely for the purpose of expediting prosecution of the instant application, the claims of the instant application have been amended to recite specific cell growth stimulating agents, bioactive agents, and biocompatible substances that are not described in the cited reference. More specifically, claim 1 has been amended to refer to biocompatible substances selected from polysaccharides, PVA sponges or lactic acid/glycolic acid polymers. Claim 2 has been amended to recite cell growth stimulating agents selected from a mutated FGF, a transcription factor, an anti-apoptotic molecule, an insulin like growth factor (IGF) family member, a vascular endothelial growth factor (VEGF) family member, a colony stimulating factor (CSF) family member, an angiopoietin family member, and an interleukin family member. Support for these amendments is provided throughout the specification and claims originally filed, and specific support for PVA sponges is provided, *e.g.*, in Example 1. In addition, claims 27, 29, 30, 32, 34, 38, 44, 46, 68, and 71, which were not rejected under Section 102, have been amended to independent format. Applicants submit that neither of the cited references teaches the recited growth stimulating agents, bioactive agents, and biocompatible substances recited in the present claims. Therefore, these references fail to teach each element of the present claims and do not anticipate the claimed

invention. In light of these amendments, Applicants respectfully request that the present bases of rejection under Section 102 be reconsidered and withdrawn.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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